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10/593,683	09/20/2006	Mingjun Huang	API-0005	9081

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EXAMINER	
WOOLWINE, SAMUEL C	
ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
03/12/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/593,683	HUANG ET AL.	
	Examiner	Art Unit	
	SAMUEL WOOLWINE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-21,23,31,33,36 and 51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,20,21,23,31,33,36 and 51* is/are rejected.

7)☒ Claim(s) *19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 September 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status

Applicant's amendment filed 12/08/2008 is acknowledged.

The rejection of claims 1-7, 14-21, 23, 31, 33, 36 and 51 under 35 U.S.C. 112, 2nd paragraph made in the Office action mailed 09/11/2008 is withdrawn in view of Applicant's amendment.

The rejection of claims 1, 6, 7 and 14-17 under 35 U.S.C. 102(b) over Hardy et al (2003) is withdrawn in view of Applicant's cancellation of these claims.

The rejection of claims 2-5 under 35 U.S.C. 103(a) based on Hardy et al (2003) is withdrawn in view of Applicant's cancellation of these claims.

Applicant's corrections to the application replacing the word "hepatosoma" with "hepatoma" are noted and accepted.

Applicant is reminded that a requirement for corrected drawing for figure 1 was made in the Office action mailed 09/11/2008 (which requirement is reiterated below).

The Office action mailed 09/11/2008 indicated allowable subject matter. This position has been reconsidered in view of the new prior art references cited below.

This action is NON-FINAL.

Drawings

The drawings filed 09/20/2006 are objected to because the three boxes in figure 1 serving as labels contain shading that obscures the text within. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should

include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 18, 23, 31, 36 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hardy et al (Journal of Virology 77(3):2029-2037, February 2003, cited on the IDS of 09/20/2006) in view of Mueller et al (Journal of Biological Chemistry 261(25):11756-11764, September 1986).

Claim 31 recites all the limitations claim 18 and the additional limitations of providing a test compound, and comparing the results to the same process lacking a test compound. Therefore, any prior art teachings that anticipate or render obvious the method of claim 31 would necessarily anticipate or render obvious the method of claim 18.

With regard to claim 31 (and claim 18), Hardy teaches a method for determining whether a test compound is an RNA synthesis initiation inhibitor of a positive strand RNA virus comprising:

contacting an isolated replicase complex for the positive strand RNA virus (Abstract: "A number of hepatitis C virus (HCV) proteins, including NS5B, the RNA-dependent RNA polymerase, were detected in membrane fractions from Huh7 cells containing autonomously replicating HCV RNA replicons. These membrane fractions were used in a cell-free system for the analysis of HCV RNA replication." Page 2031, column 2, last paragraph: "The P15 fractions enriched for HCV nonstructural proteins were assayed for replicase activity in the presence of a reaction mix...". Page 2030,

paragraph bridging columns 1-2: "…we produced membrane fractions from cells harboring the subgenomic replicon. These fractions were shown to contain several HCV nonstructural proteins and RdRp activity. This system allows cell-free analysis of RNA replication by what is predicted to be a multicomponent HCV RNA replicase."),

an isolated viral replicon template RNA for the positive strand RNA virus (Page 2031, column 1, first paragraph of "Results": "The replicon RNA…was derived from the HCV genotype 1b…". Page 2031, column 2, last paragraph: "Since no additional RNA is added to the in vitro reaction mixture, the template corresponds to the endogenous replicon RNA."),

nucleotides (Page 2031, column 2, last paragraph: "…cold nucleoside triphosphates (NTPs)…". See also last paragraph, page 2030.),

and a labeled nucleotide analog (Page 2031, column 2, last paragraph: "…including [^{32}P]CTP…". See also last paragraph, page 2030.),

and the test compound (Page 2033, column 2, last paragraph: "Membrane fractions from cells containing the HCV replicon RNA were incubated for 5 min at 25°C in the presence of candidate inhibitory compounds…".)

under conditions sufficient for in vitro RNA synthesis, to form a newly synthesized RNA population comprising the labeled nucleotide analog (Page 2033, column 2, last paragraph: "Membrane fractions from cells containing the HCV replicon RNA were incubated for 5 min at 25°C in the presence of candidate inhibitory compounds…After this preincubation period, the remaining components of the standard replication reaction were added...and the reactions continued for 1 h at 34°C.");

detecting the newly synthesized RNA population comprising the labeled nucleotide analog (See figure 7. See also Materials and Methods, paragraph entitled "In vitro HCV RNA synthesis" bridging pages 2030-2031.)*;*

quantitating the newly synthesized RNA population comprising the labeled nucleotide analog to provide a test RNA amount (See figure 7 caption: "...quantitated by using a phosphorimager...".)*;*

and comparing the test RNA amount with a control RNA amount of a control newly synthesized RNA population comprising the labeled nucleotide analog produced in the absence of the test compound (See figure 7; the graph clearly indicates a 0 μM inhibitor data point, which represents a reaction performed in the absence of the inhibitor, i.e. test compound.)

wherein a decrease in the test RNA amount compared to the control RNA amount indicates that the test compound inhibits RNA synthesis of the positive strand RNA virus (See figure 7, which indicates that the amount of test RNA, as measured by the incorporation of the labeled nucleotide, decreases with increasing concentration of inhibitor.).

With regard to claim 23, Hardy teaches radiolabeled nucleotide (page 2031, column 2, last paragraph: "…including [^{32}P]CTP…") which is directly detectable as a result of a physical property of the analog (i.e. its radioactivity).

With regard to claims 36 and 51, Hardy teaches hepatitis C virus (see entire article, e.g. abstract).

Hardy does not teach *hybridizing a probe and the newly synthesized RNA population comprising the labeled nucleotide analog, under stringent conditions, wherein the probe is complementary to at least a portion of an initiation region of the newly synthesized RNA population; digesting unhybridized, single-stranded RNA with a single-strand specific ribonuclease to form a protected RNA population comprising the labeled nucleotide analog; detecting the protected RNA population comprising the labeled nucleotide analog; quantitating the protected RNA population comprising the labeled nucleotide analog; and comparing the test RNA amount with a control RNA amount of protected RNA* to determine whether *the test compound inhibits RNA synthesis initiation of the positive strand virus*.

In other words, the difference between the claimed invention and Hardy is that Hardy does not carry out and RNase protection assay using a probe to the transcription initiation region to assess transcription *initiation* (Hardy just quantifies the final transcript).

It was known in the prior art to hybridize a probe to the transcription initiation region of a transcript followed by RNase digestion to assess transcription initiation. As in the claimed methods, Mueller synthesized newly transcribed RNA comprising a labeled nucleotide analog and hybridized the newly synthesized RNA with a probe (unlabeled), followed by digestion of the unprotected RNA.

In particular, Mueller taught an assay comprising *hybridizing a probe and the newly synthesized RNA population comprising the labeled nucleotide analog* (See page 11758, column 1, 2nd and 3rd paragraphs for the synthesis of newly synthesized RNA

population comprising a labeled nucleotide analog (i.e. ^{32}P-labeled); see page 11758, column 1, paragraph entitled "Hybridization and Digestion of the RNA/DNA Hybrid"; see paragraph bridging pages 11758-9; see page 11759, paragraph bridging columns 1-2: "The clones, serving as probes of the 21 S rDNA, 14 S rDNA, Oli-1, $tRNA^{Cys}$, and the $tRNA_f^{Met}$ genes, overlap the transcriptional promoter in each case. This allowed an assessment of the fidelity of transcriptional initiation as well as of the rates of transcription."),

under stringent conditions (see page 11758, column 1, paragraph entitled "Hybridization and Digestion of the RNA/DNA Hybrid"; the term "stringent conditions" does not distinguish over the conditions taught by Mueller),

wherein the probe is complementary to at least a portion of an initiation region of the newly synthesized RNA population (see page 11759, paragraph bridging columns 1-2: "The clones, serving as probes of the 21 S rDNA, 14 S rDNA, Oli-1, $tRNA^{Cys}$, and the $tRNA_f^{Met}$ genes, overlap the transcriptional promoter in each case. This allowed an assessment of the fidelity of transcriptional initiation as well as of the rates of transcription.");

digesting unhybridized, single-stranded RNA with a single-strand specific ribonuclease to form a protected RNA population comprising the labeled nucleotide analog (see page 11758, column 1, paragraph entitled "Hybridization and Digestion of the RNA/DNA Hybrid"; see paragraph bridging pages 11758-9);

detecting the protected RNA population comprising the labeled nucleotide analog (see page 11758, column 2, paragraph entitled "Gel Electrophoresis of the Samples");

quantitating the protected RNA population comprising the labeled nucleotide analog (see page 11758, column 2, paragraph entitled "Quantitation of the Autoradiogram").

Mueller also taught other probes upstream and downstream regions of polygenic transcription units, stating "with these probes we can determine whether attenuation occurs during transcription in these polygenic units" (see paragraph bridging columns 1-2 on page 11759). Attenuation refers to impairment of the elongation phase of transcription (e.g. see last sentence of abstract). Hence, it was already known in the prior art to distinguish between transcriptional initiation and transcriptional elongation by using probes proximal and distal, respectively, to the transcription initiation region.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Hardy by hybridizing the newly synthesized portions of the test and control transcription reactions to probes complementary to at least a portion of the initiation region of the transcripts under investigation, digest the unhybridized, single-stranded RNA with single-strand specific ribonuclease, detect and quantify the protected portions of the newly synthesized RNA as taught by Mueller in order to provide "an assessment of the fidelity of transcriptional initiation as well as of the rates of transcription."

Claims 20 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hardy et al (Journal of Virology 77(3):2029-2037, February 2003, cited on the IDS of 09/20/2006) in view of Mueller et al (Journal of Biological Chemistry 261(25):11756-

11764, September 1986) as applied to claims 18, 23, 31, 36 and 51 above and further in view of De Francesco et al (US 2002/0164722, prior art of record) and Hess et al (Methods in Enzymology 200:188-204, 1991, prior art of record).

The teachings of Hardy have been discussed. Hardy teaches *transfecting a cell line with a viral replicon RNA or a DNA template for a viral replicon to provide a transfected cell line* (page 2030, column 1, first paragraph: "In vitro transcribed replicon RNAs are electroporated into the human hepatoma cell line Huh7 and placed under selection."). Hardy implicitly teaches *incubating the transfected cell line under conditions suitable for production of viral replicase complexes*, since the membrane fraction obtained from the cells demonstrated replicase activity (page 2030, paragraph bridging columns 1-2: "…we produced membrane fractions from cells harboring the subgenomic replicon. These fractions were shown to contain several HCV nonstructural proteins and RdRp activity. This system allows cell-free analysis of RNA replication by what is predicted to be a multicomponent HCV RNA replicase.").

Hardy does not teach *isolating the replicase complexes and the viral replicon template RNA from the cell membrane fraction of the transfected cells*.

De Francesco teaches an in vitro method of reproducing the RNA-dependent RNA polymerase activity of the HCV NS5B protein (the replicase; see paragraph [0009]). De Francesco teaches that "…the recombinant proteins containing sequences of NS5B, either purified to apparent homogeneity or present in extracts of overproducing organisms, can catalyse the addition of ribonucleotides to the 3'-termini of exogenous RNA molecules…" (paragraph [0009]). Therefore, to purify the HCV

replicase to apparent homogeneity (and thus, inherently, away from a cell membrane fraction) was known in the art.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to purify the replicase *complex* from the cell membrane fraction when practicing the method suggested by the combined teachings of Hardy and Mueller, just as De Francesco taught to do with the HCV replicase. One of skill in the art would have realized that purified proteins would have been preferable to crude cell membrane fractions, a sentiment expressed by Hess et al at page 192, last full paragraph: "In most cases, the experimental advantages of working with purified proteins in a defined system, rather than with crude cell extracts, justify the additional effort necessary to purify the proteins in question."

Claims 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hardy et al (Journal of Virology 77(3):2029-2037, February 2003, cited on the IDS of 09/20/2006) in view of Mueller et al (Journal of Biological Chemistry 261(25):11756-11764, September 1986), De Francesco et al (US 2002/0164722, prior art of record) and Hess et al (Methods in Enzymology 200:188-204, 1991, prior art of record) as applied to claims 20 and 33 above and further in view of Bartenschlager (DE19915178 A1, published October 5, 2000, prior art of record). As the Bartenschlager disclosure is printed in German, US Patent 6,630,343 will be relied upon as a translation.

The teachings of Hardy, Mueller, De Francesco and Hess have been discussed. These reference do not teach that the DNA template for the viral replicon is SEQ ID NO:1.

Bartenschlager teaches HCV constructs for introducing into cells in order to provide autonomously replicating HCV RNA templates (see DE19915178, page 3, lines 37-46, which correlates with US Patent 6,630,343, column 3, line 66 through column 4, line 14). One of the constructs taught is Bartenschlager's SEQ ID NO:4 (see DE19915178, page 4, lines 16-21, which correlates with US Patent 6,630,343, column 5, lines 26-33), which is 100% identical to Applicant's SEQ ID NO:1.

It would have been *prima facie* obvious to one of ordinary skill in the art to use the construct taught by Bartenschlager as the "subgenomic replicon" in the method of Hardy, since this sequence was designed by Bartenschlager specifically to provide HCV replicon RNA. One of skill in the art would have considered such a modification nothing more than substituting one HCV RNA replicon construct for another. See MPEP 2144.06 regarding the obviousness of substituting equivalents.

Conclusion

Claim 19 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The only apparent reason for using 2'-O-methyl-5-methyluridine-5'-triphosphate known in the art would have been for the purpose of conferring increased resistance to nuclease degradation (e.g. see previous rejection of claim 2, beginning on page 8 of the Office action mailed 09/11/2008). However, one would not have been inclined to modify the method suggested by the combined teachings of Hardy and Mueller to include this nucleoside analog, because Mueller's technique *required* the RNase degradation of the RNA (i.e. that portion not protected by the probe). Applicant's specification indicates that the addition of this analog increases the yield of the transcription product (page 16, paragraph [0049] and page 29, paragraph [0089] of the specification submitted 09/20/2006). This advantage was not taught or suggested in the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL WOOLWINE whose telephone number is (571)272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samuel Woolwine/
Examiner, Art Unit 1637